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EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,234	PROUDFOOT ET AL.	
	Examiner	Art Unit	
	Ian Dang	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18 and 20-22* is/are pending in the application.

4a) Of the above claim(s) *13,14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,15,16 and 20-22* is/are rejected.

7)☒ Claim(s) *11,12,15,16 and 20-22* is/are objected to.

8)☒ Claim(s) *11-18 and 20-22* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: Exhibit A

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the species CCL5/RANTES and the species autoimmune hepatitis in the communication filed on 10/05/2007 is acknowledged.

The traversal is on the ground that the claims are all linked by a special technical feature that involves the reduced GAG-binding activity associated with the claimed CC-chemokine mutants.

Applicant's arguments have been fully considered but are not found persuasive. As disclosed in the Office action mailed 09/05/2007, the species listed in claims 12-14 and 22 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: CC-chemokine mutants in claims 12-14 do not share common structural and functional features. Each CC-chemokine mutant has a distinct amino acid sequence and function. In addition, the claimed CC-chemokine mutants requires additional modifications, such as deletions, insertions, or substitutions of amino acids, leading to additional structural and functional changes. Under PCR Rule 13.1, the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

It is noted that each species listed in the previous Office action is independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required.

The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments and/or Claims

The amendment of 05 October 2007 has been entered in full. Claims 1-10 and 19 have been cancelled. Claims 13-14 and 17-18 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/05/2007.

Claims 11, 12, 15, 16, and 20-22 are pending and under examination as they read upon the elected species of CCL5/RANTES and autoimmune hepatitis.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The disclosure is objected to because of the following informalities:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. For instance, a new title may recite "the CC-chemokine CCL5/RANTES mutant against liver diseases".

Appropriate correction is required.

Claim Objections

Claims 11-12, 15-16, and 20-22 objected to because of the following informalities:

Claims 11-12, 15-16, and 20-22 use acronyms without first defining what they represent in the independent claims (see for example, "GAG", "CC-chemokine", etc.). While the claims

can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 (Second paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-12, 15-16, and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-12, 15-16, 20-22 are indefinite because the elements recited in claim 11 do not constitute proper Markush groups. The claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. (See especially claim 1) See MPEP § 2173.05(h).

Claims 11-12, 15-16, and 20-22 are indefinite because the claims have a step that does not clearly relate back to the preamble. For example, the preamble of claim 11 recites "a method for the treatment of liver fibrotic inflammatory and/or liver autoimmune diseases". However, there is no step in the body of the claim indicating that the treatment has taken place.

Claim 22 recites the limitation "liver disease". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112 (Written Description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-12, 15-16 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 11 is drawn to the treatment of liver fibrotic inflammatory or liver autoimmune diseases comprising the administration of a CC-chemokine mutant having reduced GAG-binding activity, wherein the CC-chemokine is CCL5/RANTES. Claims 15 and 16 are drawn to an active variant of a CC-chemokine mutant in which one or more amino acids have been inserted, deleted, or substituted in a conservative manner. Claim 20 is directed to an amino acid sequence belonging to a protein sequence other than the corresponding CC-chemokine.

First, the Examiner has broadly interpreted the terms "liver fibrotic inflammatory diseases" and "liver autoimmune diseases" as any liver diseases associated with inflammation.

In addition, the Examiner has broadly interpreted claims 11, 15-16, and 20 as reading upon any variants, derivatives, and fragments of a CC-chemokine mutant having reduced GAG-binding activity wherein the chemokine is CCL5/RANTES. Specifically, the specification teaches that any other corresponding mutant of CCL3 / MIP-1 alpha, CCL4 / MIP-1 beta, or CCL5 / RANTES having reduced GAG-binding properties resulting from the substitution of the same residues disclosed in the prior art but with a different amino acid (i.e. the basic residue is

substituted with a non-polar amino acid other than Ala or with an acid residue), or resulting from a substitution in other position(s) can be used according to the invention (page 6, lines 1-6).

Moreover, the specification teaches that the mutation at the specific positions leading to the decreased affinity for GAGs, the CC-chemokine mutants may include other modifications with respect to the wild-type molecule, generating active variants of said CC-chemokine mutants in which one or more amino acids have been added, deleted, or substituted in a conservative manner (page 7, lines 6-8). Other additional preferred changes in these active variants are commonly known as "conservative" or "safe" substitutions, that is, with amino acids having sufficiently similar chemical properties, in order to maintain the structure and the biological function of the CC-chemokine mutant. It is clear that insertions and deletions of amino acids may also be made in the above defined sequences without altering their function, particularly if the insertions or deletions only involve a few amino acids, e.g., under ten, and preferably under three, and do not remove or displace amino acids 20 which are critical to the functional conformation of a protein or a peptide (page 7, lines 8-10).

Finally, the specification teaches that a polypeptide comprising the GAG-binding defective CC-chemokine mutant and an amino acid sequence belonging to a protein sequence other than the corresponding CC-chemokine can be also used for treating liver fibrotic inflammatory and/or autoimmune diseases. The heterologous sequence is intended provide additional properties without considerably impairing the therapeutic activity. Examples of such additional properties are an easier purification procedure, a longer lasting half-life in body fluids, an additional binding moiety, the maturation by means of an endoproteolytic digestion, or extracellular localization (page 8, line 23 to page 9, line 2). Additional protein sequences can be chosen amongst extracellular domains of membrane-bound protein, immunoglobulin constant

regions, multimerization domains, extracellular proteins, signal peptide-containing proteins, export signal-containing proteins (page 9, lines 12-15).

Thus, the claims are genus claims. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Specifically, the specification does not clearly define liver fibrotic inflammatory diseases; liver autoimmune diseases; variants, derivatives, or fragments of a CCL5/RANTES mutant having reduced GAG-binding activity; an amino sequence belonging to a protein sequence other than the corresponding CC-chemokine; and all methods of using such. Thus, the scope of the claims includes numerous structural and functional variants, and the genus' are highly variant because a significant number of structural and functional differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural and functional features that could distinguish liver fibrotic inflammatory diseases; liver autoimmune diseases; variants, derivatives, and fragments of a CCL5/RANTES mutant having reduced GAG-binding activity; amino sequences belonging to a protein sequence other than the corresponding CC-chemokine are missing from the disclosure. No common attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, liver fibrotic inflammatory diseases; liver autoimmune diseases; variants, derivatives, and fragments of a CCL5/RANTES mutant having reduced GAG-binding activity; an amino sequence belonging to a protein sequence other than the corresponding CC-chemokine; and all methods of using such are insufficient to describe the genus.

The written description requirement for a claimed genus' may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus for liver fibrotic inflammatory diseases; liver autoimmune diseases; variants, derivatives, fragments of a CCL5/RANTES mutant having reduced GAG-binding activity; an amino sequence belonging to a protein sequence other than the corresponding CC-chemokine; and all methods of using such.

There is no description of the special features, which are critical to the structure and function of the genus claimed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the liver fibrotic inflammatory diseases; liver autoimmune diseases; variants, derivatives, and fragments of a CCL5/RANTES mutant having reduced GAG-binding activity; and an amino sequence belonging to a protein sequence other than the corresponding CC-chemokine encompassed by the claims. Thus, no identifying characteristics or properties of the claimed liver fibrotic inflammatory diseases; liver autoimmune diseases; variants, derivatives, and fragments of a CCL5/RANTES mutant having reduced GAG-binding activity; and amino sequence belonging to a protein sequence other than the corresponding CC-chemokine are provided such that one of skill would be able to predictably identify the encompassed variant biological and chemical entities recited in the instant claims. One of skill in the art would reasonably conclude that the

disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 112 (Enablement)

Claims 11-12, 15-16, and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing serum alanine amino transferase (ATL) in a subject with hepatitis comprising the administration of the CCL5/RANTES mutant triple 40's of SEQ ID NO:1 does not reasonably provide enablement for a method of treatment of liver fibrotic inflammatory and/or liver autoimmune diseases comprising the administration of an effective amount of any CC-chemokine mutant having reduced GAG-binding activity wherein the CC-chemokine is CCL5/RANTES. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breath of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

Nature of the invention and breath of the claims

The invention is drawn to a method of treatment of liver fibrotic inflammatory and/or liver autoimmune diseases comprising the administration of an effective amount of any CC-chemokine mutant having reduced GAG-binding activity wherein the CC-chemokine is CCL5/RANTES. The invention is broad because claims 11-12, 15, 16, and 20-21 encompass a large number of liver diseases and a large number of mutant polypeptides.

Specifically, the specification teaches that any other corresponding mutant of CCL3 / MIP-1 alpha, CCL4 / MIP-1 beta, or CCL5 / RANTES having reduced GAG-binding properties resulting from the substitution of the same residues disclosed in the prior art but with a different amino acid (i.e. the basic residue is substituted with a non-polar amino acid other than Ala or with an acid residue), or resulting from a substitution in other position(s) can be used according to the invention (page 6, lines 1-6).

In addition to the mutation at the specific positions leading to the decreased affinity for GAGs, the CC-chemokine mutants may include other modifications with respect to the wild-type molecule, generating active variants of said CC-chemokine mutants in which one or more amino acids have been added, deleted, or substituted in a conservative manner (page 7, lines 6-8). Other additional preferred changes in these active variants are commonly known as "conservative" or "safe" substitutions, that is, with amino acids having sufficiently similar chemical properties, in order to maintain the structure and the biological function of the CC-chemokine mutant. It is clear that insertions and deletions of amino acids may also be made in the above defined sequences without altering their function, particularly if the insertions or deletions only involve a few amino acids, e.g., under ten, and preferably under three, and do not remove or displace amino acids which are critical to the functional conformation of a protein or a peptide (page 7, lines 8-10).

Finally, the specification teaches that a polypeptide comprising the GAG-binding defective CC-chemokine mutant and an amino acid sequence belonging to a protein sequence other than the corresponding CC-chemokine can be also used for treating liver fibrotic inflammatory and/or autoimmune diseases. The heterologous sequence is intended provide additional properties without considerably impairing the therapeutic activity. Examples of such additional properties are an easier purification procedure, a longer lasting half-life in body fluids, an additional binding moiety, the maturation by means of an endoproteolytic digestion, or extracellular localization (page 8, line 23 to page 9, line 2). Additional protein sequences can be chosen amongst extracellular domains of membrane-bound protein, immunoglobulin constant regions, multimerization domains, extracellular proteins, signal peptide-containing proteins, export signal-containing proteins (page 9, lines 12-15).

Unpredictability and state of the art

The state of the art for the triple 40's and 50's RANTES mutants are well known, but the state of the art for a CC-chemokine mutant having reduced GAG-binding activity, and homologs, variants, derivatives, or fragments of the triple 40s mutant of SEQ ID NO:1 are not well characterized. It is noted that the triple 40's RANTES mutants correspond to the triple mutation of the cluster of basic residues with alanine residues in the 40s loop of the chemokine RANTESwhile the triple 50's RANTES mutants correspond to the triple mutation of the cluster of basic residues with alanine residues in the 50s loop of the chemokine RANTES.

For instance, the reference by Proudfoot et al., an inventor of the instant application, (2001, Journal of Biological Chemistry, Volume 276, Issue 14, pages 10620-10626) teach that the mutations of the cluster of basic residues, ^{44}RKNR^{47} with alanine residues reduced the selectivity of RANTES binding to different GAGs. Moreover, the resulting mutant or the triple

40s mutant is able to inhibit HIV-1 infectivity (page 10620, abstract). However, the reference does not teach any substitutions other than with alanine residues to generate variants or homologues of the triple 40s mutant. In addition, the mutations of the cluster of basic residues, ^{55}KKWVR^{59} with alanine residues has no effects on the binding of RANTES to GAGs. The triple 50's cluster mutation caused no significant difference in activity compared to the wild type sequence (page 10620, abstract).

However, the art is silent regarding derivatives for a CC-chemokine mutant having reduced GAG-binding activity or the triple 40's RANTES mutant of SEQ ID NO:1. For instance, the specification teaches that in order to perform structure-function analysis of CC-chemokines, variants containing substitutions or chemical modifications in different internal positions, as well as CC-chemokine derived peptides, have been tested for the interactions with receptors or other molecules (page 2, lines 19-23). However, the specification does not disclose any distinguishing characteristics for derivatives or fragments of a CCL5/RANTES mutant having reduced GAG-binding activity or fragments and derivatives of the triple 40's RANTES mutant of SEQ ID NO:1. The variants, derivatives, or fragments of the amino acid of SEQ ID NO:1 are not well characterized in the specification or the state of the art. Applicant has not provided any guidance as to what amino acid residues can be added, substituted, or deleted to/from SEQ ID NO:1 or from CCL5/RANTES while retaining the ability of the polypeptide having reduced GAG-binding activity.

The variants, derivatives, or fragments of a CCL5/RANTES mutant having reduced GAG-binding activity or variants, derivatives, or fragments of the triple 40's RANTES mutant of SEQ ID NO:1 are not well characterized in the specification. Applicant has not provided any guidance as to what amino acid residues can be added, substituted, or deleted to/from the polypeptide while retaining the ability to treat liver fibrotic inflammatory or liver autoimmune

disease. For instance, the specification teaches that insertions and deletions of amino acids may also be made in the above defined sequences without altering their function, particularly if the insertions or deletions only involve a few amino acids, e.g., under ten, and preferably under three, and do not remove or displace amino acids which are critical to the functional conformation of a protein or a peptide (page 7, lines 8-10) encompassing an infinite number of changes to a CC-chemokine mutant having reduced GAG-binding activity or the triple 40's RANTES mutant of SEQ ID NO:1. Each amino acid change to a CCL5/RANTES mutant having reduced GAG-binding activity or to the triple 40's RANTES mutant homologue results in distinct structure, function, and biological activity, and the combination of any of these amino acid changes may result in distinct mutant characteristics. The teachings in the specification provide general characteristics of these domains but the specification does not provide any distinguishing or specific characteristics for any of these CC-chemokine mutant variants having reduced GAG-binding activity or triple 40's RANTES mutant variants of SEQ ID NO:1 required for a method for the treatment of liver diseases.

Applicant has not provided any distinguishing characteristics for any of the protein variants and fragments encompassed by the claims. Undue experimentation would be required of one skilled in the art to be able to make/use the claimed methods of the instant application.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-

dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which

fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The state of the art teaches that liver disease is synonymous with cirrhosis of the liver, which is caused by scar tissue replacing normal healthy tissue and blocking the flow of blood through the organ. Cirrhosis has many causes including alcoholic liver disease, chronic hepatitis (C, B, and C), and autoimmune hepatitis. Autoimmune hepatitis is caused by the immune system attacking the liver and causing inflammation, damage, and eventually scarring and cirrhosis (see Exhibit A).

Furthermore, a recent review teaches that the state of the art regarding autoimmune liver disease is not predictable because the phrase "autoimmune liver disease" encompasses numerous distinct disorders and their causes are not known. For instance, the reference by Washington (2007, Modern Pathology, Volume 20, pages S15-S30) teaches that there are three main categories of autoimmune liver disease: autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholantis (PSC); all are well-defined entities with diagnosis based upon a constellation of clinical serologic, and liver pathology findings. Although these diseases are considered autoimmune in nature, the etiology and possible environmental triggers of each remain obscure (page S15, Abstract).

Moreover, the state of the art indicates that no reliable animal model exists for autoimmune disorders in the liver, such as autoimmune hepatitis (AIH). For instance, Christen et al. (2007, Autoimmunity Reviews, Volume 6, pages 306-311) teach that induction of autoimmunity seems more difficult to achieve in the liver than other organs, such as the pancreas, where mouse models for (autoimmune) type 1 diabetes are well established (page 309, last paragraph). In addition, Christen et al. (2007) further teach that several attempts have been made to develop a reliable animal model that reflects the persistent hepatic destruction

that occurs in human AIH. However, most models were only successful in causing a transient form of hepatic damage and often used rather complex ways of disease induction (page 306, abstract).

In view of these teachings in the art and the limited guidance provided in the specification, a method for reducing serum alanine amino transferase (ATL) in subjects with hepatitis comprising the administration of the CCL5/RANTES mutant triple 40's of SEQ ID NO:1 is not predictable for a method of treatment of liver fibrotic inflammatory and/or liver autoimmune diseases comprising the administration of an effective amount of any CC-chemokine mutant having reduced GAG-binding activity wherein the CC-chemokine is CCL5/RANTES.

The amount of direction or guidance present

Applicants' disclosure is limited to the structural description of the full-length amino acid of SEQ ID NO:1. However, the specification does not provide guidance or direction regarding all possible CCL5/RANTES mutants having reduced GAG-binding activity or any variants, derivatives, or fragments of the amino acid sequence of SEQ ID NO:1. For instance, the specification teaches that in order to perform structure-function analysis of CC-chemokines, variants containing substitutions or chemical modifications in different internal positions, as well as CC-chemokine derived peptides, have been tested for the interactions with receptors or other molecules (page 2, lines 19-23), but does not disclose any distinguishing characteristics for derivatives or fragments of a CCL5/RANTES mutant having reduced GAG-binding activity or the triple 40's RANTES mutant of SEQ ID NO:1. The variants, derivatives, or fragments of the amino acid of SEQ ID NO:1 are not well characterized in the specification or the state of the art. Applicant has not provided any guidance as to what amino acid residues can be added, substituted, or deleted to/from CCL5/RANTES or SEQ ID NO:1 while retaining the ability of the polypeptide to have reduced GAG-binding activity.

In addition, the specification teaches that mutation at the specific positions leading to the decreased affinity for GAGs, the CC-chemokine mutants may include other modifications with respect to the wild-type molecule, generating active variants of said CC-chemokine mutants in which one or more amino acids have been added, deleted, or substituted in a conservative manner (page 7, lines 6-8). However, Applicant has not provided any guidance as to what amino acid residues can be added, substituted, or deleted to/from SEQ ID NO:1 while retaining the biological activity of the claimed triple 40's RANTES mutant as disclosed in Example 1.

Moreover, the specification doe not provide guidance regarding the disorders encompassed by liver autoimmune diseases. For instance, the specification teaches that liver specific inflammation is mediated by activated CD4(+) T cells and driven by an upregulation of the hepatic expression of IFNgamma, but the mechanisms governing T cell migration from the blood into tissues during T cell-mediated hepatitis remains incompletely understood, since the endogenous mediators that promote the recruitment of T cells to the liver during T cell mediated liver diseases have been poorly characterized (page 3, lines 17-22).

Finally, the specification does not provide any guidance for the treatment of particular symptoms of a liver disease with the administration of the triple 40's mutant or how decreased levels of alanine transferase (ALT) correlate with the treatment of a liver disease.

Working Examples

Although Applicants have provided examples for the biological activities for the full-length triple 40's RANTES mutant of SEQ ID NO:1 by measuring serum of alanine transferase in a mice (Example 1), the specification does not provide any methods or working examples with other CC-chemokine mutant having reduced GAG-binding activity or other triple 40's RANTES mutant of SEQ ID NO:1, or homologs, derivatives, variants, or fragments for CC-

chemokine mutant having reduced GAG-binding activity or the triple 40's RANTES mutant of SEQ ID NO:1. In addition, the specification does not provide any working example for the treatment of a particular liver disease with the administration of the triple 40's mutant in an animal model. Finally, the specification does not provide any example for the treatment of particular symptoms of a liver disease or how levels of alanine transferase correlate with the treatment of a liver disease.

The quantity of experimentation needed

Without sufficient disclosure in the specification, it would require undue experimentation for one of skill in the art to be able to make/use any triple 40's RANTES mutant homologs and any derivatives, variants, and fragments of the amino acid sequence of SEQ ID NO:1. In addition, it would require undue experimentation to practice the invention commensurate in scope with the claims because, the claims are broadly drawn to any triple 40's RANTES mutant homologs and any derivatives, variants, and fragments of the amino acid sequence of SEQ ID NO:1.

Finally, a large quantity of experimentation would also be required to associate a nexus between a treatment for liver disease with a CC-chemokine mutant having reduced GAG-binding activity and a reduction of serum alanine amino transferase (ATL) in a hepatitis mice model with the administration of the triple 40s RANTES mutant. Undue experimentation would be required of the skilled artisan to determine the variants, analogues and fragments for a CCL5/RANTES mutant having reduced GAG-binding activity or the triple 40's RANTES mutant of SEQ ID NO:1 as required by the claims. The specification has not provided any identifying characteristics for the CC-chemokine mutant having reduced GAG-binding activity or the triple 40's RANTES mutant of SEQ ID NO:1 in order to treat liver diseases.

Conclusion

No claim is allowed.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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October 26, 2007

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